SUPPORT FOR THE AMENDMENTS

Support for an array of biolayers each having a defined perimeter is found on page 85, second paragraph; page 87, second paragraph and figures 15 and 16.

REMARKS

Claims 144 -151 remain pending in the application.

The present invention relates to an array of biolayers made by microdispensing a controlled volume of liquid onto a surface to form an array of biolayers where each biolayer has a defined perimeter separate from others in the array.

Claims 144 – 149 are rejected under 35 USC 102(b) as being anticipated by Dattagupta et al.(US 4,542,102). Claims 144 – 147 and 150 – 151 are rejected under 35 USC 102 (b) over Lowe et al. US 4,562,157)

The Examiner asserts that both Dattagupta et al. and Lowe et al. disclose an "array of biolayers" within the broadest reasonable interpretation of the claims. However, both reference rely on photolithographic methods. Thus, the Examiner's argument can only apply to the present invention if the product-by-process language is given no weight (i.e., "array provided by dispensing a controlled volume of liquid".) However, the product-by-process language is critical to the success of the invention and should not be read out of the claims. A device formed by microdispensing a controlled volume of liquid is not functionally equivalent to a similar one made by the photolithographic methods of Dattagupta et al. and Lowe et al.

For instance, photolithography generally provides only for covalent means of attaching a ligand to a surface. This restricts surface coverage to essentially a monolayer of ligand. Such a thin coverage can provide insufficient ligand to generate a detectable signal at the sensor, and so impairs sensitivity of the device.

Furthermore, given the instability of many ligands disclosed by Lowe, a monolayer would limit the sensitivity (detection limit) of the device. It would also limit the duration the sensor could be used, and could also reduce its shelf life. These factors are not problems for the present invention, which provides layers up to microns in thickness (and thus provides plenty of ligand) and operates reliably in many conditions, see jointly owned US 5,112,455. It also provides a method of manufacture with adequate shelf-life, where the time from manufacture of a device to the time it is used by a customer may be many months.

Lowe can only make sensors with surfaces that are chemically amenable to covalent attachment of a ligand. The present invention permits layers to be formed on a broader range of surfaces, i.e. those that permit non-covalent adhesion.

Lowe requires a photoactivation step for ligand immobilization, whereas the present invention does not. This is advantageous in commercial sensor manufacture, where additional steps incur additional cost.

Lowe requires a whole sequence of wet chemistry steps to achieve ligand immobilization. The present invention can be accomplished by a single microdispensing step alone, or with a prior plasma treatment. The latter is much simpler and of great advantage in a commercial manufacturing process.

Both the cited references teach a synthetic sequence of reactions occurring on a solid surface, to form a covalently bound layer. In Dattagupta et al. the entire solid support is covered, whereas in Lowe et al. the synthesis occurs at a specific location based on light activation through a mask. Both describe immobilization of bioactive molecules.

The rejections in effect argue that any way of immobilizing a bioactive molecule is equivalent to photolithography . However, both Dattagupta et al. and Lowe et al. are silent on ways for placing a portion of liquid in a controlled location on a surface. In Dattagupta et al. the entire surface is coated. To the extent that in Lowe et al. covalent coupling occurs at a desired location on a surface, this appears to be done by exposing the entire surface to a liquid and then using a mask and light to control the location of a coupling reaction. Unreacted material from elsewhere on the surface is presumably removed in a washing step.

Both Dattagupta et al.and Lowe et al. are also silent on microdispensing, dispensing, pipetting and any other synonyms of the method of the present invention and thus are completely silent on "microdispensing a controlled volume of liquid... onto a...surface". Neither reference therefore anticipates or makes obvious our disclosure.

The limitation of "microdispensing a controlled volume of liquid" is not functionally equivalent to the way the devices in Dattagupta et al. and Lowe et al. are fabricated. It is distinct and has several advantages not found in the prior art. By using microdispensing, a biolayer can be formed at a predetermined location on a surface and with controlled geometry, including diameter and *thickness*, (see

section 5.4., starting at page 105, line 21). This provides for economy with expensive reagents. It requires a microdispensing system (see page 106, line 25 to page 107, line 24) to dispense an exact amount or volume, of liquid with a controlled composition onto a surface with a controlled surface energy. Note the volume can be controlled to a precision of about 5% (see page 106, line 8).

The combination of a controlled composition of the liquid, including surface tension, hydrophobicity and hydrophilicity, as described in section 5.4.1.2. (starting at page 109, line 20) and the controlled surface energy (see section 5.4.1.3. starting at page 111, line 20), serve to control the spreading of the liquid on the surface before it dries. This results in biolayers of a defined perimeter and thickness, which could not be achieved by photolithographic methods.

Note that the disclosed microdispensing apparatus permits exact positioning of a microsyringe tip in the x, y and z directions and also rotation theta, with respect to the surface. In the x and y directions, the precision is to within 13 microns (see page 106, line 3). This permits even relatively thidk biolayers to be formed on a surface at exactly predetermined locations. It also permits the formation of an array of biolayers in an exact predetermined pattern, as a wafer prober of the type disclosed (page 106, line 27) is equipped with a step and repeat feature in the x-y plane. For example, the biolayer can be microdispensed on each of a square array of indicator electrodes repeated several hundred times on a silicon wafer surface (see page 101, line 7). None of these aspects of the present invention are anticipated or obvious in view of the teaching in Dattagupta et al. and Lowe et al., either individually or in combination.

The present method also has genuine utility and has been used to microfabricate arrays of sensors for a medical diagnostic system sold in the USA and around the world. Information is available at Product Info - www.i-stat.com

To further distinguish the over the cited references, claim 144 has been amended to recite an array of biolayers where each biolayer has a defined perimeter separate from each other biolayer in the array. Note that language relating to a defined perimeter was recited in a divisional application, US 6,306,594 and claims relating to a method of microdispensing were allowed in divisional US 5,554,339.

Applicants submit that the case is now in condition for allowance. Early notification of such action is earnestly solicited.

Please charge any shortage in fees due in connection with the filing, or credit any overpayment to Deposit Account No. 50-1710.

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